I. SUBSTITUTE SPECIFICATION

Applicants again thank Examiner Saoud for entering the substitute specification, as indicated in the Office Action of March 15, 2000 (Paper No. 23).

II. CLAIM OBJECTIONS

The Examiner's objections to claims 73-81 have been addressed in the above amendment. Consequently, these objections should be withdrawn and claims 73-81 should be allowed.

III. REJECTIONS UNDER 35 USC § 112

The Examiner rejects claims 38-56, 57-72, 82-101 and 114-120 and 132-141 under 35 USC § 112, first paragraph, for the alleged reason that:

> ...because the specification, while being enabling for KGF and KGF polypeptides which have an amino acid sequence as set forth in Figure 7, or is truncated within the region of amino acids 32-78, does not reasonably provide enablement for any protein that (1) has a recited molecular weight, produced by fibroblast cells and has a specific activity as recited in the claims or (2) comprises a segment of the amino acid sequence of Figure 7.

Office Action of March 15, 2000, Paper No. 23, page 4, paragraph 7

The Examiner explains that the specification does not enable any person skilled in the art to which it pertains to use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection as it may apply to the claims, as amended above.

In response, applicants have amended claims 38, 49 and 114 to recite "amino acids 79-189 of Figure 7 and a sufficient number of consecutive amino acids 32-78 of Figure 7 to confer epithelial cell specificity." Applicants also have added new claims 147-149, which similarly recite specific amino acid sequences. The Examiner has acknowledged that the specification enables a polypeptide comprising less than all of amino acids 32-78 of Figure 7. Applicants also have amended claims 57 and 82 to clarify that the recited "segment" comprises a sufficient

number of consecutive amino acids to confer **epithelial cell specificity**. In view of this amendment, applicants respectfully request the Examiner to withdraw this rejection.

In paragraph 8, the Examiner states that the specification does not enable claims 49-56, 82-110 and 121-131 because it fails to describe the amount of KGF needed to provide the recited activity. However, the Examiner further indicates that "[c]laims to a method of stimulating epithelial cell growth, in a patient, wherein the patient has a wound, wherein the patient has an epithelial cell condition, etc. would be enabled by the specification." (Page 5, last paragraph). In view of this statement, applicants have amended claim 82 so as to recite a method of stimulating epithelial cells in wound tissue. Therefore, claim 82 and claims dependent therefrom should be allowable. However, this amendment is not a concession that the Examiner's rejection is proper. Accordingly, applicants maintain claim 49 as being directed to a method of accelerating or improving the healing of a wound.

The Examiner contends that "without knowing what amount to administer and for what length of time, one of ordinary skill in the art would not be able to practice the invention as claimed" (Page 6, line 4). However, applicants assert that it was well within the skill of the art at the time of the invention to make such a determination without undue experimentation. Such assertion is supported by Applicants' specification at page 7, lines 23-31 and page 21, lines 3-11. The invention of claim 49 involves applying a composition to a wound. The amount of the composition and the protocol for treatment would vary depending upon the nature of the wound and the subject. One of skill in the art would know this and would readily adjust the treatment accordingly, based on the teachings in Applicants' specification. This type of adjustment is a matter of routine procedure and would not rise to the level of undue experimentation. In view of these comments, and applicants' ample arguments and evidence submitted in previous responses, applicants respectfully request the examiner to withdraw this rejection.

The Examiner further contends that "...the fact that KGF can be inhibited *in vitro* does not provide for the method of treating a patient having an epithelial skin condition by inhibition" because "[t]here is no evidence to support the conclusion that all epithelial skin conditions are caused by an over expression of KGF, and therefore, could be treated by inhibition of KGF."

(Page 6, first paragraph). Applicants assume that these comments are directed to claims 121 and 126 only, as these are the claims reciting methods of treating an epithelial skin condition. In response, applicants point out that these claims also recite quite clearly that only conditions caused by over expression of KGF are within the scope of the claim; both of these claims refer to treating " an epithelial skin condition caused by over expression of Keratinocyte Growth Factor (KGF)." Therefore, the Examiner's observation that not all epithelial skin conditions are caused by over expression of KGF is simply irrelevant to what applicants are claiming in claims 121 and 126. Additionally, applicants point out that routine methods exist to determine whether a condition is, in fact, characterized by over-expression of KGF. For instance, at the time of the invention, it was routine to apply immunohistochemical, in situ techniques (i.e, hybridization or RT-PCR) to biopsies in order to evaluate the expression of a given molecule. In view of this explanation, applicants respectfully request the Examiner to reconsider her position and withdraw this grounds of rejection.

The Examiner also has stated again that "[t]here are no examples in the instant specification that inhibition of KGF will provide a therapeutic treatment for any known condition of the skin" and that "[t]here is no specific method disclosed that would enable an artisan to practice the method as claimed." First, applicants again point out that the invention is not directed to treatment of just "any known condition of the skin;" it is directed to treating conditions associated with over expression of KGF. (See page 8, line 13-page 9, line 2). Secondly, as the Examiner is aware, it is not necessary under U.S. Patent law to exemplify the invention. In their specification, Applicants have shown the correlation between KGF and stimulation of epithelial cells. Applicants also have disclosed antibodies that neutralize KGF activity in an *in vitro* assay. They teach the production of the antibodies and the assay for determining which antibodies neutralize KGF activity (page 42, line 26 to page 43, line 26). The post-filing date art that applicants have previously submitted to the Examiner confirm what applicants had taught in their specification. In that regard, applicants again direct the examiner to the work of Alarid *et al, Proc. Natl. Acad. Sci. USA* 91: 1074-1078 (1994) (copy previously attached), which describes the use of KGF-neutralizing monoclonal antibody to inhibit seminal

vesical growth and morphogenesis in organ cultures and to the work of Sugimura, *Int. J. Devl. Biol.* 40: 941-951 (1996), which show the use of neutralizing antibodies against KGF in the inhibition of cell growth and morphogenesis in the rat prostate (copy previously attached). Applicants teach that anti-KGF antibodies can inhibit KGF stimulation of epithelial cells. They describe the generic invention and the enabling tools for practicing this invention with different types of epithelial cells, of which there are many. With regard to the Examiner's contention that the specification fails to teach the methods for practicing the invention, applicants again respectfully traverse. Applicants have shown the production of anti-KGF antibodies and the assay for determining whether they neutralizing KGF activity. The development of pharmaceuticals for application to a skin condition was well within the skill of the art, without undue experimentation, at the time of the invention.

The Examiner also has stated that "[t]he claimed method encompasses the use of an antibody (any antibody) against KGF to specifically inhibit epithelial cells, however, other factors (especially aFGF) also stimulate epithelial cells." (Page 7) She further asserts that "[i]t has not been established that the inhibition of a single growth factor would be effective for inhibiting epithelial cells and a person of ordinary skill in the art would not reasonably expect that the mere inhibition of KGF would result in inhibition of epithelial cells." In response, applicants point out that claim 110 is directed to the inhibition of KGF activity. Therefore, the activity of other factors is not relevant. With regard to claims 121 and 126, applicants assert that the claims are directed to treating conditions related to the over expression of KGF. Thus, the existence of other factors that stimulate epithelial cells is also irrelevant. In any event, the Examiner's concerns are based primarily upon speculation and thus, the Examiner has failed to meet the burden of establishing that the claimed invention could not function on account of the existence of other growth factors.

Finally, with regard to the Examiner's general comments about the state of immunotherapy art, applicants again direct the Examiner's attention to Weiner, "An Overview of Monoclonal Antibody Therapy of Cancer" *Seminars in Oncology*, 26: 41-50 (1999) and Weiner, "Monoclonal Antibody Therapy of Cancer" *Seminars in Oncology* 26: 43-51 (1999),

which support the use of antibodies in clinical settings. As stated previously, this literature should resolve any doubt about the potential efficacy of antibodies for use within the scope of the claimed invention.

The Examiner rejects claims 121-131, reasserting that the specification fails to enable the use of a DNA probe in the claimed methods. Applicants respectfully traverse but have amended the claims to exclude this embodiment so as to further the allowance of these claims.

The Examiner rejects claims 133, 135, 137, 139 and 141 under 35 USC § 112, second paragraph, for not reciting how the cellular response is measured. Applicants have amended these claims pursuant to the Examiner's suggestion and therefore respectfully request the withdrawal of this rejection.

CONCLUSION

Applicants note that the Examiner has indicated that claims 111-113 are allowable. Applicants respectfully assert that in view of the above amendment and explanations, all the remaining pending claims also are in condition for allowance. Indication of allowability of all the claims is therefore respectfully solicited.

Respectfully submitted,

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Date

Patricia D. Granados
Reg. No. 33,683

Customer ID No. 26633
HELLER EHRMAN WHITE & MCAULIFFE LLP
1666 K Street, NW, Suite 300
Washington, DC 20006-1228
(202) 912-2000 (telephone)
(202) 912-2020 (telecopier)

MARKED UP COPY OF CLAIMS AS AMENDED

38. (Twice Amended) A method of stimulating epithelial cells comprising administering to a patient in need thereof an epithelial cell stimulating amount of a glycosylated or unglycosylated keratinocyte growth factor (KGF) polypeptide, wherein said polypeptide comprises (a) amino acids 79-189 of Figure 7 and (b) a sufficient number of consecutive amino acids 32 –78 of Figure 7 [and has a molecular weight of between about 16 and about 30 kDa, as calculated by SDS PAGE under reducing conditions, and] to confer on said polypeptide epithelial cell specificity [has mitogenic activity on BALB/MK keratinocyte cells].

49. (Twice Amended) A method of accelerating or improving the healing of a wound involving tissue of epithelial origin, said method comprising administering to the wound site of a patient, an epithelial cell stimulating amount of a glycosylated or unglycosylated keratinocyte growth factor (KGF) polypeptide, wherein said polypeptide comprises (a) amino acids 79-189 of Figure 7 and (b) a sufficient number of consecutive amino acids 32 –78 of Figure 7 [and has a molecular weight of between about 16 and about 30 kDa, as calculated by SDS PAGE under reducing conditions, and] to confer on said polypeptide epithelial cell specificity [has mitogenic activity on BALB/MK keratinocyte cells].

57. (Twice Amended) A method of stimulating epithelial cells comprising administering to a patient in need thereof an epithelial cell stimulating amount of a glycosylated or unglycosylated keratinocyte growth factor (KGF) polypeptide comprising the amino acid sequence of Figure 7, or a segment of said sequence, wherein said segment comprises a sufficient number of consecutive amino acids 32-78 of Figure 7 to confer on said polypeptide [mitogenic activity on BALB/MK keratinocyte cells] epithelial cell specificity.

73. (Amended) [The] A method of [claim 57, wherein said polypeptide comprises] stimulating epithelial cells comprising administering to a patient in need thereof an epithelial cell

stimulating amount of a glycosylated or unglycosylated keratinocyte growth factor (KGF) polypeptide comprising amino acids 32-194 of Figure 7.

82. (Twice Amended) A method of [accelerating or improving the healing of a wound involving tissue of epithelial origin] stimulating epithelial cells in wound tissue, the method comprising administering to [the] said wound [site of a patient] tissue an epithelial cell stimulating amount of a glycosylated or unglycosylated keratinocyte growth factor (KGF) polypeptide comprising the amino acid sequence of Figure 7 or a segment of said sequence, wherein said segment comprises a sufficient number of consecutive amino acids 32-78 of Figure 7 to confer on said polypeptide [mitogenic activity on BALB/MK keratinocyte cells] epithelial cell specificity.

114. (Twice Amended) A method of stimulating epithelial cells *in vitro* comprising contacting epithelial cells with an epithelial cell stimulating amount of a glycosylated or unglycosylated keratinocyte growth factor (KGF) polypeptide, wherein said polypeptide comprises (a) amino acids 79-189 of Figure 7 and (b) a sufficient number of consecutive amino acids 32 –78 of Figure 7 [and has a molecular weight of between about 16 and about 30 kDa, as calculated by SDS PAGE under reducing conditions, and] to confer on said polypeptide epithelial cell specificity [has mitogenic activity on BALB/MK keratinocyte cells].

121.(Twice Amended) A method of treating [a patient having] an epithelial skin condition caused by over-expression of Keratinocyte Growth Factor (KGF), comprising topically applying to [the] skin effected by said condition [of said patient], a therapeutically effective amount of a compound, wherein in an *in vitro* bioassay, said compound inhibits a Keratinocyte Growth Factor (KGF) protein [having] comprising the amino acid sequence of Figure 7 from stimulating epithelial cell mitogenesis, wherein said compound comprises an active ingredient that is selected from the group consisting of an anti-KGF antibody[,]and a fragment of [an] said antibody[, and a DNA probe].

126. (Twice Amended) A method of treating a patient having an epithelial skin condition caused by over-expression of Keratinocyte Growth Factor (KGF) comprising administering to said patient a therapeutically effective amount of a compound [to treat said condition], wherein in an *in vitro* assay, said compound inhibits a Keratinocyte Growth Factor protein [having] comprising the amino acid sequence of Figure 7 from stimulating epithelial cell mitogenesis, wherein said compound comprises an active ingredient that is selected from the group consisting of an anti-KGF antibody[,] and a fragment of [an] said antibody [and a DNA probe].

129. (Twice Amended) A method of inhibiting a Keratinocyte Growth Factor from stimulating epithelial cells in an *in vitro* medium comprising applying a compound to said medium, wherein in an *in vitro* bioassay, said compound inhibits a Keratinocyte Growth Factor [having] comprising the amino acid sequence of Figure 7 from stimulating epithelial cell mitogenesis wherein said compound comprises an active ingredient that is selected from the group consisting of an antibody[,] and a fragment of an antibody [and a DNA probe].

133. (Amended) The method of claim 38 or claim 147, wherein five nanomolar of said polypeptide elicits less than one-fold stimulation over background in NIH/3T3 cells, as measured by percent of maximal H^3-thymidine incorporation.

135. (Amended) The method of claim 49 or 138, wherein five nanomolar of said polypeptide elicits less than one-fold stimulation over background in NIH/3T3 cells, as measured by percent of maximal H^3-thymidine incorporation.

137. (Amended) The method of claim 57, wherein five nanomolar of said polypeptide elicits less than one-fold stimulation over background in NIH/3T3 cells, as measured by percent of maximal H^3-thymidine incorporation.

139. (Amended) The method of claim 82, wherein five nanomolar of said polypeptide elicits less than one-fold stimulation over background in NIH/3T3 cells, as measured by percent of maximal H^3-thymidine incorporation.

141. (Amended) The method of claim 114 or 149, wherein five nanomolar of said polypeptide elicits less than one-fold stimulation over background in NIH/3T3 cells, as measured by percent of maximal H^3-thymidine incorporation.